Trials@uspto.gov
571.272.7822

Paper No. 16
Entered: June 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENZYME CORPORATION,
Petitioner,

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owner.

Case IPR2016-00383
Patent 6,331,415 B1

Before LORA M. GREEN, ERICA A. FRANKLIN, and SUSAN L. C. MITCHELL, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Genzyme Corporation ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–4, 9, 11, 12, 14–20, and 33 of U.S. Patent No. 6,331,415 B1 (Ex. 1001, "the '415 patent"). Paper 2 ("Pet."). Genentech, Inc. and City of Hope (collectively "Patent Owner") filed a Preliminary Response. Paper 10. In addition, after authorization from the Board (Paper 11), Petitioner filed a Reply to the Preliminary Response. Paper 12.

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon considering the Petition and the Preliminary Response, we determine that Petitioner has failed to demonstrate a reasonable likelihood that it would prevail in showing the unpatentability of any of the challenged claims. Accordingly, we decline to institute an *inter partes* review.

A. Related Proceedings

Petitioner identifies IPR2015-01624, which was filed by Sanofi-Aventis U.S. LLC ("Sanofi") and Regeneron Pharmaceuticals, as challenging claims in the '415 patent. Pet. 58. Trial was instituted in IPR2015-01624 on February 5, 2016. IPR2015-01624, Paper 15.

Patent Owner identifies also several district court and PTO proceedings related to the '415 patent. Paper 6.

B. The '415 Patent (Ex. 1001)

The '415 patent issued on December 18, 2001, and claims priority to an application filed on April 8, 1983, now U.S. Patent No. 4,816,567. *See*

Ex. 1001, Title Page. Shmuel Cabilly, Herbert L. Heyneker, William E. Holmes, Arthur D. Riggs, and Ronald B. Wetzel are the listed co-inventors. *Id.*

The '415 patent relates generally to processes for producing immunoglobulin molecules in a host cell transformed with a first DNA sequence encoding the variable domain of the heavy chain and a second DNA sequence encoding the variable domain of the light chain, as well as vectors and transformed host cells used in such processes. *Id.*, Abstract. More specifically, the first and second DNA sequences are present in either different vectors or in a single vector, and independently expressed so that the immunoglobulin heavy and light chains are produced as separate molecules in the transformed single host cell. *See id.*, cols. 1, 15, 18, 21, and 33.

According to the Specification of the '415 patent, there were two major sources of vertebrate antibodies that could be generated *in situ* by the mammalian B lymphocytes or in cell culture by B-cell hybrids (hybridomas). *Id.* at 1:42–45. The Specification notes, however, that monoclonal antibodies produced by these two sources suffer from disadvantages, including contamination with other cellular materials, instability, production of an undesired glycosylated form, high cost, and an inability to manipulate the genome. *Id.* at 2:40–66. The Specification recognizes that "the use of recombinant DNA technology can express entirely heterologous polypeptides—so-called direct expression—or alternatively may express a heterologous polypeptide fused to a portion of the amino acid sequence of a homologous polypeptide." *Id.* at 4:33–37.

The Specification states that "[t]he invention relates to antibodies and to non-specific immunoglobulins (NSIs) formed by recombinant techniques using suitable host cell cultures," which can "be manipulated at the genomic level to produce chimeras of variants which draw their homology from species which differ from each other." *Id.* at 4:53–59. The Specification further indicates that "[t]he ability of the method of the invention to produce heavy and light chains or portions thereof, in isolation from each other offers the opportunity to obtain unique and unprecedented assemblies of immunoglobulins, Fab regions, and univalent antibodies." *Id.* at 12:52–62.

C. Illustrative Claims

Petitioner challenges claims 1–4, 9, 11, 12, 14–20, and 33 of the '415 patent. Claims 1, 15, 18, and 33 are independent. Independent claims 1 and 18 are illustrative, and are reproduced below:

> 1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of:
>
> (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and
>
> (ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.
>
> 18. A transformed host cell comprising at least two vectors, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an immunoglobulin light chain.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–4, 9, 11, 12, 14–20, and 33 of the '415 patent on the following grounds (Pet. 3):

References	**Basis**	**Claims Challenged**
Salser[1]	§ 102(e)	1–4, 9, 11, 12, 15–20, and 33
Salser and Ochi[2]	§ 103(a)	1–4, 9, 11, 12, 14–20, and 33
Salser and Southern[3]	§ 103(a)	2, 18, and 20

Petitioner relies also on the Declaration of Margaret H. Baron, M.D., Ph.D. Ex. 1058.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the Specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, No. 15–446, 2016 WL 3369425, at *12 (U.S. June 20, 2016) (upholding the use of the broadest reasonable interpretation standard). Under the broadest reasonable

---

[1] Salser et al., U.S. Patent No. 4,396,601, issued Aug. 2, 1983 (Ex. 1002) ("Salser").

[2] Ochi et al., *Transfer of a Cloned Immunoglobulin Light-Chain Gene to Mutant Hybridoma Cells Restores Specific Antibody Production*, 302 NATURE 340–42 (1983) (Ex. 1003) ("Ochi").

[3] P.J. Southern and P. Berg, *Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter*, 1 J. MOLECULAR AND APPLIED GENETICS 327–341 (1982) (Ex. 1004) ("Southern").

construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We determine that, for purposes of this Decision, none of the terms in the challenged claims require express construction at this time. *See, e.g.*, *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy).

B. 35 U.S.C. § 325(d)

Patent Owner argues Sanofi is a real party-in-interest in both the instant proceeding, as well as IPR2015-01624. Prelim. Resp. 9. Patent Owner asserts that the prior art relied upon by Petitioner in this case were discussed in the Petition in IPR2015-01624, and were submitted also as exhibits to that Petition. *Id.* Patent Owner, therefore, contends that Sanofi cannot represent that those references were unknown to it at the time of filing of the Petition in IPR2015-01624. *Id.*

Patent Owner additionally asserts that the grounds proffered by the instant Petition are substantially the same as the challenges raised in the petition in IPR2015-01624. *Id.* at 12–15. Patent Owner argues further that the Petition in the instant proceeding has the benefit of Patent Owner's Preliminary Response in IPR2015-01624, and that we should not allow Petitioner in this proceeding "a second bite of the apple." *Id.* at 15–20. Patent Owner, thus, requests that we exercise our discretion under 35 U.S.C. § 325(d) and deny the Petition. *Id*. at 5.

35 U.S.C. § 325(d) states, in relevant part (emphasis added), that "[i]n determining whether to institute or a proceeding under this chapter . . . the Director *may* take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." We have considered the Patent Owner's arguments, along with the facts and circumstances of the instant proceeding, and we decline to exercise our discretion to deny the Petition under 35 U.S.C. 325(d).

C. Anticipation by Salser (Ex. 1002)

Petitioner contends that claims 1–4, 9, 11, 12, 15–20, and 33 are anticipated by Salser. Pet. 26–47. Patent Owner disagrees. Prelim. Resp. 37–52.

i. Overview of Salser (Ex. 1002)

Salser discloses "[m]ethods and compositions . . . for providing mammalian hosts with additional genetic capability, either a novel capability or enhancement of an existing one." Ex. 1002, 1:46–49. Host cells that are capable of regeneration are removed from the host, and genetic material is introduced such that the genetic material "becomes capable of replication and expression." *Id.* at 1:49–52. "The introduced genetic material includes at least one marker which allows for selective advantage for the host cells in which the introduced genetic material is capable of expression." *Id.* at 1:52–56. In particular, the genetic material provides for the expression of an enzyme. *Id.* at 1:62–64. Salser teaches further that

> genetic functions can be provided for a variety of purposes including treatment of genetic deficiencies, which includes providing a genetic capability which the host lacks or production of a normal product where the host produces an abnormal one; production of enzymes which can protect the host from cytotoxic

> agents; or for production of a wide variety of proteins e.g. hormones, globulins or the like.

Id. at 2:29–36.

As to the genetic material that may be introduced, Salser teaches:

> The genetic material which is employed for recombination with the host cells may be either naturally occurring, synthetic, or combinations thereof. Depending upon the mode employed for introduction, the size of the genetic material introduced will vary. Furthermore, when two or more genes are to be introduced they may be carried on a single chain, a plurality of chains, or combinations thereof. Restrictions as to the size of a DNA fragment will be as a result of limitations due to the technical aspects of the vector: if a recombinant DNA is to be used, by the packaging requirements of a viral vector; the probability of transfer into the recipient cells by the method employed; the manner of preparation and isolation of the DNA fragments; or the like.

Id. at 3:46–59.

As to the type of DNA, Salser teaches:

> [T]he types of DNA which will be employed for selective markers include genes which react with drugs which interfere with regeneration so as to destroy activity of the drug; genes which provide sites which are not susceptible to drug action, so as to prevent the drug's action in the particular cell; genes which are repetitive for production of a desired protein e.g. an enzyme, which is inhibited by the drug; or genes which affect the regulatory function of the cell, so as to provide for overproduction of a particular enzyme by the natural processes of the cell, and which increase the normal replication of the cell genes to enable the cell to better compete for limited resources within the body.

Id. at 4:54–66.

Salser teaches also that the "DNA employed may provide for a single gene, a single set of genes, e.g. the beta-globin gene cluster, or a plurality of unrelated genes." *Id.* at 5:27–29. Salser discloses that "[w]ith the

hemoglobinopathies, insertion of a normally regulated and structurally normal β-globin gene should be capable of correcting the defect in β-thalassemia and sickle cell disease." *Id.* at 17:23–26.

According to Salser:

> The transfer of genes for drug resistance to hematopoietic cells in vitro and their selection in intact animals in vivo provides for a variety of clinical applications. Such applications include the transfer of drug resistance genes with the objective of enabling patients with cancer to tolerate higher doses of anti-neoplastic drugs and insertion of genes which confer a proliferative advantage coupled to other genes to treat human genetic diseases such as the hemoglobinopathes.

Id. at 17:6–33.

ii. Analysis

"Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim." *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Nonetheless, "a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); *see also In re Preda*, 401 F.2d 825, 826 (CCPA 1968) (noting that "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom").

"Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). "The requirement that the prior art elements themselves be 'arranged as in the claim' means that claims cannot be 'treated . . . as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning.'" *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (quoting *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1459 (Fed. Cir. 1984)).

"It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Rather, "whether a generic disclosure necessarily anticipates everything within the genus . . . depends on the factual aspects of the specific disclosure and the particular products at issue." *Sanofi–Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008). Of "critical importance" in conducting this analysis is "how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology." *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012). One way that a genus may be narrowed is that the prior art discloses a "'pattern of preferences'" that leads to the claimed species. *Sanofi–Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006). Moreover, the reference "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without

any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972).

a. Claim 1

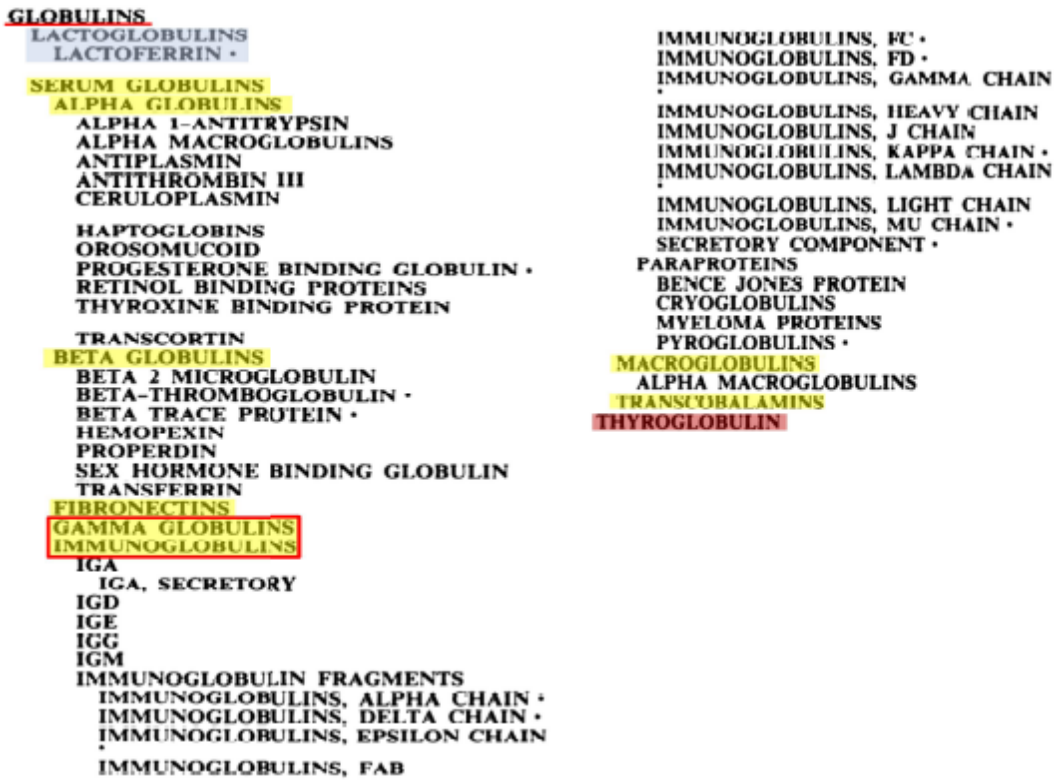
Independent claim 1 requires the recombinant production of an immunoglobulin molecule (i.e., an antibody) or immunologically functional fragment by "independently expressing" DNA sequences encoding at least the variable domains of the immunoglobulin heavy and light chains within a "single host cell." As to independent claim 1, Petitioner contends that Salser "discloses a process for producing an immunoglobulin molecule in a single host cell." Pet. 33. Specifically, Petitioner asserts that Salser "provides a method for producing a 'wide variety of proteins' using rDNA technology . . . among which are 'globulins.'" *Id.* (citing Ex. 1002, 2:29–36; Ex. 1058 ¶ 63).

According to Petitioner, the ordinary artisan, upon considering the genus of "globulin proteins" as of April 1983, "would have immediately and primarily envisioned the species of immunoglobulins within the genus of globulins." *Id.* Petitioner asserts that the family of mammalian globulins that would have been considered as targets for the gene replacement therapy of Salser is defined and limited, with no more than eight members. *Id.* at 33–34 (citing Ex. 1058 ¶ 64). Petitioner asserts:

> The Medical Subject Headings index,[4] the controlled vocabulary for indexing articles and cataloging books and other holdings in the National Library of Medicine, identifies three distinct sub-genus members of the globulin family: lactoglobulins

[4] Petitioner argues that the Medical Subject Headings index is extrinsic evidence as to how the ordinary artisan would have understood the term "globulin." Pet. 34–35.

> (lactoferrin), serum globulins, and thyroglobulin. Serum globulins are further broken down into six species: immunoglobulins (gamma globulins), alpha-globulins, beta-globulins, fibronectins, macroglobulins, and transcobalamins:



Pet. 34 (citing Ex. 1012, 256–57; Ex. 1058 ¶ 64) (citations omitted) (footnote added).

Petitioner asserts further that of the globulins identified in the Medical Subject Headings index, immunoglobulins would have been understood to be the most important from a medical and therapeutic standpoint, as they are necessary for a properly functioning immune system. *Id.* at 35 (citing Ex. 1058 ¶ 65). According to Petitioner, the "sole conceptual difference" between Salser and the '415 patent "is that Salser's cell factory is returned to a host whereas the '415 patent's cell factory remains *ex vivo*." Pet. 27. Petitioner asserts, however, that the function of both cells is to produce

recombinant proteins that are encoded by inserted foreign genes. *Id.* (citing Ex. 1058 ¶ 59).

Patent Owner responds that Salser does not teach recombinant immunoglobulins, and in fact, does not disclose immunoglobulins at all. Prelim. Resp. 37. Petitioner, Patent Owner contends, "mischaracterizes the 'genus' disclosed in Salser." *Id.* at 38. Specifically, Patent Owner notes that the genus of Salser "consists of all hormones, all globulins, and all 'like' proteins, not simply a genus of 'globulins.'" *Id.* (citing Ex. 1002, 2:34–35). That genus, Patent Owner asserts, is vast. *Id.* And even if one were to consider only the genus of globulins, that genus includes 40 species of proteins, including "11 types of alpha globulins, 7 types of beta globulins, multiple different types of immunoglobulins and fragments, and several other subspecies of 'globulin' proteins." *Id.* (citing Ex. 1012, 256–57).

Moreover, Patent Owner contends that "Petitioner has not demonstrated that Salser would direct one of ordinary skill in the art to immunoglobulins specifically." *Id.* Petitioner, Patent Owner asserts, ignores the fact that Salser focused specifically on treatments for hemoglobin-based genetic deficiencies, which were, at the time of Salser, important topics of investigation. *Id.* at 41 (citing Ex. 1002, 17:14; Ex. 2010, 7).

We agree with Patent Owner that Petitioner has not persuasively established that the ordinary artisan, when reading Salser's genus of proteins, which could be a target of the disclosed methods, would "at once envisage" the species of "immunoglobulins" as required by challenged claim 1, even with the specific mention of the subgenus of "globulins." See *Kennametal, Inc.*, 780 F.3d 1376 at 1381.

As noted by Patent Owner, the genus of Salser is not limited to globulins. Prelim. Resp. 38. Rather, Salser teaches:

> genetic functions can be provided for a variety of purposes including treatment of genetic deficiencies, which includes providing a genetic capability which the host lacks or production of a normal product where the host produces an abnormal one; *production of enzymes* which can protect the host from cytotoxic agents; or for *production of a wide variety of proteins e.g. hormones, globulins or the like*.

Ex. 1002, 2:28–36 (emphasis added). And when Salser does focus on globulins, the focus is on the beta-globin gene for the treatment of hemoglobinopathies. *Id.* at 5:27–29, 17:6–33. Thus, Salser does not express a pattern of preferences such that the ordinary artisan would envision the use of DNAs encoding for immunoglobulin heavy and light chains in the gene therapy methods taught by that reference.

We have considered the Declaration of Dr. Baron, as well as the Medical Subject Headings index, but they do not convince us otherwise. Petitioner relies on the Medical Subject Headings index to support its contention that the family of mammalian globulins that would have been considered as targets for the gene replacement therapy has no more than eight members. Pet. 33–34. Moreover, Dr. Baron opines:

> among the globulins identified in the Medical Subject Headings at the time, immunoglobulins were inarguably the most important of the globulins from a medical and therapeutic standpoint. Certainly immunoglobulins, and specifically antibodies, are an important and necessary component of a properly functioning immune system. And immunoglobulins were the subject of intense research and experimental focus before 1983 and remain so to this day. . . . This is reflected by their respective frequency of citation in the indexed literature in the U.S. National Library of Medicine's "PubMed" database from the beginning of the 20th century until April 1983.

Ex. 1058 ¶ 65.

As already discussed, the genus of Salser is not limited to globulins, but includes enzymes and hormones and the like. Ex. 1002, 2:28–36. Petitioner and its expert do not point us to any teaching in Salser upon consideration of the large genus of proteins, including enzymes, hormones, globulins and the like, that would have provided a pattern of preferences leading to the species of immunoglobulins.

Petitioner contends further that Salser "discloses transforming a single host cell with two DNA sequences, encoding the immunoglobulin heavy and light chains." Pet. 36. In particular, Petitioner notes that Salser teaches the transformation of mammalian cells with DNA that is capable of replication and expression in the host cell. *Id.* (citing Ex. 1002, 1:49–52; Ex. 1058 ¶¶ 67–68). As taught by Salser, the DNA includes a selectable marker, and may also contain other genetic material for the production of a wide variety of proteins. *Id.* at 37 (citing Ex. 1002, 2:15–18, 1:29–36; Ex. 1058 ¶ 68). According to Petitioner, Salser discloses that the "full complement of genetic material to be incorporated into the host cell by transformation can therefore include 'two or more genes,' 'a single set of genes' or a 'plurality of unrelated genes' in addition to the selectable marker, and they can be 'carried on a single chain, a plurality of chains, or combinations thereof.'" *Id.* at 37–38 (citing Ex. 1002 3:46–53, 5:26–29; Ex. 1058 ¶ 68). Petitioner asserts that "[t]hese are all unmistakable references to multiple *different* genes of interest." *Id.* at 38 (footnote omitted).

In particular, Petitioner points to Salser's discussion that a single set of genes, such as the beta-globin gene cluster, may be transformed into a host cell. *Id.* at 29. Petitioner notes that as the beta-globin gene cluster is

five separate genes encoding five different polypeptides, wherein each gene is separated by non-coding DNA, expression of the cluster would result in five separate polypeptide molecules being expressed. *Id.* at 29–30.

Therefore, Petitioner asserts that the disclosure of Salser "clearly accommodates the insertion into the cell of the two (heavy and light chain) DNA sequences that were known to [an ordinary artisan] in 1983 to be required to make an immunoglobulin." *Id.* at 39 (citing Ex. 1058 ¶ 69). Petitioner contends "it takes no more than [an ordinary artisan's] ordinary creativity to understand as a matter of simple logic that producing an immunoglobulin in a single host cell transformed with a vector having 'two or more genes' (or a 'single set of genes' or a 'plurality of unrelated genes') requires that both heavy and light chain DNA sequences be present in the single transformed host cell." *Id.* at 40 (citing Ex. 1058 ¶ 70). According to Petitioner:

> [T]he Salser patent's teaching to co-express heavy and light chains in a single host cell—from the disclosure of producing "globulins" by transforming a host cell with "two or more genes," "a single set of genes" or a "plurality of unrelated genes"—is in line with the inventors' goal of creating a gene-based treatment for subjects who cannot make, or make an incorrect version of, an immunoglobulin with therapeutic value; to produce the chains in separate cells and remove them from a common environment where they can assemble *in vivo* into a functional (antigen-binding) immunoglobulin would completely vitiate the intended goals of the Salser invention.

Id. at 40–41 (citing Ex. 1058 ¶ 70).

Patent Owner responds that Salser does not disclose the transformation of a single host cell with multiple DNA sequences that encode immunoglobulin heavy and light chains. Prelim. Resp. 43. Patent Owner characterizes Petitioner's challenge as arguing that "Salser's

disclosure of 'genes' (plural) 'clearly accommodates' the 'insertion into the cell of the two (heavy and light chain) DNA sequences . . . required to make an immunoglobulin.'" *Id.* (quoting Pet. 39). "[A]ccommodating" such functionality as argued by Petitioner, Patent Owner asserts, does not meet the standard for anticipation. *Id*. Specifically, Patent Owner contends "Petitioner has only argued that the various disclosures ***could have*** been arranged by one of ordinary skill in the art in April 1983," which is insufficient for anticipation. *Id.* at 43–44.

According to Patent Owner, Petitioner has "cobbled together different passages from disparate parts of the disclosure" of Salser, by attempting to link the disclosure of introducing DNA of two or more genes to Salser's disclosure of globulins. *Id.* at 44. Nothing in Salser, Patent Owner asserts, "discusses the transfection of a single host cell with multiple genes of interest with the goal of making a functional multimeric protein." *Id.*

Patent Owner argues that Salser's reference to the beta-globin gene cluster does not help Petitioner's anticipation challenge. *Id*. at 47. Patent Owner argues that the articles cited in the Petition teach that "the beta-globin gene cluster is made up of variants of ***the same gene*** that are expressed at ***different*** times during human development, *i.e.*, all five genes are not expressed together in nature." *Id.* (citing Ex. 1031, 853–854; Ex 1032, 855–856; Ex. 2012, 3930–3931; Ex. 2013, 1589). Petitioner, therefore, according to Patent owner, "has not shown that its citation to beta-globin discloses independent expression of multiple different proteins at the same time." *Id.*

Moreover, Patent Owner argues that Salser's reference to beta-globin is not a reference to the transformation of a cell with two different exogenous genes of interest, with assembly of those genes into a multimeric

protein. *Id.* at 47–48. Rather, Salser's reference to beta-globin in Salser is related to providing a structurally normal beta-globin gene for treating sickle cell anemia, which is caused by a mutation in hemoglobin beta chain. *Id.* at 48. Hemoglobin, however, consists of two alpha and two beta chains. *Id.* (citing Ex. 2012, 3927). Thus, Patent Owner contends that, at best, Salser is suggesting exogenous introduction of only one of the components of hemoglobin, while the alpha chain is endogenous to the host organism. *Id.*

We agree with Patent Owner that Petitioner has not also persuasively established that Salser teaches or suggests transforming a single host cell with two DNA sequences encoding the immunoglobulin heavy and light chains. Therefore, we agree that Petitioner has failed to persuasively establish that Salser anticipates challenged claim 1 because that limitation is missing from Salser's teaching as well. Although Salser teaches that two or more genes may be introduced into a host cell, and that those genes may be carried on a single chain, a plurality of chains, or combinations thereof (Ex. 1002, 3:46–59), that teaching, along with Salser's teaching that the genes may be a single set of genes or unrelated genes (*id.* at 5:27–29), does not amount to a teaching that genes encoding for both the immunoglobulin heavy and light chains must be incorporated into the same vector or otherwise expressed within a single host cell. *See Arkley*, 455 F.2d at 587.

Moreover, Petitioner's reliance on Salser's teaching that the DNA may encode the beta-globin cluster is equally unpersuasive. As noted by Patent Owner (Prelim. Resp. 47), the beta-globin gene cluster is made up of variants of the same gene, which are not expressed together at the same time.

Such understanding is supported, for example, by Levings,[5] which teaches that the "five genes of the human β-globin locus are arranged in a linear array on chromosome 11 and are expressed in a developmental stage-specific manner in erythroid cells." Ex. 2013, 1589; *see also* Ex. 1031, 853–854 (noting that the β-globin gene is expressed exclusively in red blood cells at specific times in their development). Neither Petitioner nor its expert explain how the ordinary artisan would envision the expression of an immunoglobulin heavy and light chain DNA sequences after reading Salser disclosure of the beta-globin gene cluster, which results in the expression of five separate polypeptides at different times. We, thus, determine that Petitioner has not sufficiently established that Salser teaches, either expressly or inherently, all of the limitations as arranged in challenged claim 1.

b. Remaining Claims

In its challenge of the process of independent claim 33, and the composition of independent claims 15 and 18, Petitioner relies on the teaching of Salser as discussed above with respect to independent claim 1. Pet. 44–45. Petitioner presents also a claim chart demonstrating where it asserts the limitations added by the dependent claims 2–4, 9, 11, 12, 16, 19, and 20 are taught. *Id.* at 46. Petitioner, however, does not address the deficiencies of Salser as discussed above. Thus, Petitioner has not sufficiently demonstrated a reasonable likelihood of success in showing that claims 2–4, 9, 11, 12, 15–20, and 33 are anticipated by Salser.

[5] P. Levings and J. Bungert, *The Human β-globin Locus Control Region*, 268 EUR. J. BIOCHEM. 1589–99 (2002) (Ex. 2013) ("Levings").

iii. Conclusion

For the reasons set forth above, we determine that Petitioner has not established a reasonable likelihood that claims 1–4, 9, 11, 12, 15–20, and 33 are anticipated by Salser.

D. Obviousness over Salser (Ex. 1002) and Ochi (Ex. 1003)

Petitioner contends that claims 1–4, 9, 11, 12, 14–20, and 33 are rendered obvious by the combination of the Salser and Ochi. Pet. 47–51. Patent Owner disagrees. Prelim. Resp. 52–58.

i. Overview of Ochi (Ex. 1003)

Ochi is titled "Transfer of a cloned immunoglobulin light-chain gene to mutant hybridoma cells restores specific antibody function." Ex. 1003. Ochi teaches that the "expression of immunoglobulin (Ig) genes is regulated at several levels," noting that "some cell types do not permit immunoglobulin production." *Id.*, Abstract. For example, production of the κ chain (i.e., light chain) of the immunoglobulin requires rearrangement to juxtapose variable and joining segments, but that rearrangement alone is not sufficient for κ-chain gene expression. *Id.* According to Ochi, the "mechanisms responsible for the regulation of the expression of rearranged immunoglobulin genes are poorly understood," and that identification of the structural features for gene expression *in vitro* requires the use of cells that normally allow immunoglobulin production. *Id.*

Specifically, Ochi teaches that the Sp603 hybridoma produces IgM that is specific for the hapten 2,4,6-trinitrophenyl ("TNP"). *Id.* at 340. Ochi teaches that the "rearranged gene encoding the TNP-specific κ chain (κ_{TNP}) has been cloned." *Id.* Ochi teaches that the igk-14 mutant cell line does not produce the κ_{TNP} chain, but produces the TNP-specific μ heavy chain;

therefore, expression of the κ_{TNP} chain in those cells would be expected to allow for production of TNP-specific IgM. *Id.* Ochi reports that the κ_{TNP} chain is produced in the transformed cells and is capable of restoring IgM production. *Id.*, Abstract.

ii. Analysis

The legal question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In *KSR Int'l Co. v. Teleflex Inc.*, the Supreme Court stated that, under certain circumstances, an invention may be found obvious if *trying* a course of conduct would have been considered obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. 398, 421 (2007). In this regard, "[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).

As the court noted in *Kubin*, "[t]he Supreme Court's admonition against a formalistic approach to obviousness in this context actually

resurrects this court's own wisdom in *In re O'Farrell* . . . ." *Id.* at 1359. In *O'Farrell*, the court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under § 103. First, obviousness is not shown when

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

O'Farrell, 853 F.2d at 903. Second, obviousness is also not shown when

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id.

a. Claims 1–4, 9, 11, 12, 15–20, and 33

Petitioner asserts that to the extent that Salser's teaching of the genus of globin proteins does not anticipate the claimed immunoglobulin species of claims 1–4, 9, 11, 12, 15–20, and 33, Ochi remedies that deficiency by teaching immunoglobulins. Pet. 47–48. According to Petitioner, Ochi discloses that a mammalian host cell may be transformed with an exogenous immunoglobulin light chain DNA sequence, and that the expressed light chain can assemble with the endogenous immunoglobulin light chain to form an immunoglobulin that can bind to its antigen. *Id.* at 48. Petitioner asserts that the teaching of Ochi "of the immunoglobulin species, when considered in view of the 'globulin' genus in Salser, would render claims 1–4, 9, 11, 12, 15–20, and 33 obvious." *Id.* (citing Ex. 1058 ¶ 80).

Petitioner contends further that the ordinary artisan would have had a reason to combine Salser with Ochi with a reasonable expectation of success of achieving the claims invention. *Id.* at 48–49 (citing Ex. 1058 ¶ 81). In particular, Petitioner asserts that both Salser and Ochi are drawn "to the use of rDNA techniques to make heterologous proteins, and in particular, the same type of heterologous protein (globulins/immunoglobulins, or chain or chains thereof)"; "Salser instructs the use of plasmid vectors containing viral components and protoplast fusion transformation to this end, and [Ochi] employs such a vector construct and transformation technique in expressing the foreign light chain"; and Salser would have suggested to the ordinary artisan "to investigate publications to find instances of expressing specific globulins using rDNA technology facilitated by similar techniques (vectors and protoplast fusion)," which would have led to Ochi. *Id.* at 49 (citing Ex. 1058 ¶ 81).

Petitioner argues further that the ordinary artisan would have also selected the immunoglobulin species from the disclosure of globulins in Salser given Ochi's success in expressing an immunoglobulin light chain. *Id.* (citing Ex. 1058 ¶ 82). According to Petitioner, Ochi provides a reasonable expectation of success by teaching the assembly of expressed exogenous light chain with the endogenous heavy chain to produce an antibody that can bind to its antigen. *Id.* at 50 (citing Ex. 1058 ¶ 82).

Patent Owner responds that

> even if the Board accepts Petitioner's strained argument that Salser teaches co-expressing multiple recombinant genes in a single host cell (which it does not), a person of skill in the art would not have been motivated to combine that teaching with Ochi with any reasonable expectation of successfully expressing exogenous heavy and light chain DNA to yield a functional

antibody.

Prelim. Resp. 54.

Patent Owner argues that Petitioner does not provide a reason to combine Ochi with Salser, given Salser's focus on gene replacement therapy for blood disorders. *Id.* at 53–54. Moreover, Patent Owner asserts that Ochi does not suggest co-transforming with an exogenous heavy chain as well as an exogenous light chain. *Id.* at 54. Patent Owner argues that "[g]iven Ochi's limited disclosure of inserting an exogenous light chain to study regulatory pathways, Petitioner has articulated no reason why a person of skill in the art would reasonably expect that exogenous heavy and light chain genes could be introduced into a host cell to produce a functional antibody." *Id.* at 56.

According to Patent Owner, it is Petitioner's burden to demonstrate a reasonable expectation of success, but that Petitioner has turned that burden "on its head," as Petitioner's position is that there is no reason to believe that immunoglobulins would not be amenable to production by rDNA means. *Id.* Patent Owner argues that "Petitioner offers no basis for why the person of ordinary skill in the art reasonably ***would*** have expected the combination of Salser and Ochi to result in the assembly of a functional antibody." *Id.*

We agree with Patent Owner that Petitioner has not sufficiently established that the combination of Salser and Ochi renders challenged claims 1–4, 9, 11, 12, 15–20, and 33 obvious. Petitioner's reason to combine is premised on its assertion that in view of the globulin species of Salser, the ordinary artisan would have looked at Ochi, who teaches the recombinant production of a species of globulin, that is, an immunoglobulin. As noted by Patent Owner (Prelim. Resp. 53–54) and admitted by Petitioner (Pet. 27), the focus of Salser is on gene therapy (Ex. 1002, 1:24–28). Thus,

Salser discusses providing a genetic capability, such as the production of a normal gene product when a cell produces an abnormal one, or the production of enzymes that protect the host from cytotoxic agents. Ex. 1002, 2:29–35. In particular, Salser notes that its method may be used to treat human genetic diseases such as hemoglobinopathes. *Id.* at 17:13–14. Salser does not specifically discuss the use of the method for the production of an immunoglobulin.

Ochi looks at the ability of a cloned light chain that is expressed in immunoglobulin-producing hybridoma cells to restore specific antibody production. Ex. 1003, Abstract. The antibody studied is an IgM specific for TNP. *Id.* at 340. There is no discussion of any therapeutic use of that antibody, nor is there a discussion of therapeutic uses of antibodies in general. Except for its statement that because Salser teaches the globulin genus, and an immunoglobin as taught by Ochi is a species of that genus, Petitioner does not provide a reason why the ordinary artisan would have looked to the anti-TNP IgM of Ochi for use in the gene therapy methods of Salser.

At best, Petitioner's expert makes the statement, when discussing the anticipation challenge over Salser, that "immunoglobulins were inarguably the most important of the globulins from a medical and therapeutic standpoint." Ex. 1058 ¶ 65. Petitioner's expert, however, provides no support for that statement. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."). Moreover, neither Petitioner nor its expert point to any evidence that at the time of invention of the '415 patent

that the ordinary artisan was looking at immunoglobulins as targets of gene therapy.

As for a reasonable expectation of success, Petitioner contends that is provided by Ochi, who teaches that introduction of an exogenous light chain into an immunoglobulin producing cell allows for assembly with the endogenous heavy chain to produce a functioning antibody. That teaching of Ochi, however, does not provide a reasonable expectation of success of introducing both an exogenous light chain and heavy chain into a cell to produce a therapeutic antibody *in vivo* as required by Salser.[6]

We determine, therefore, that Petitioner has not sufficiently demonstrated that the ordinary artisan would have had a reason to combine the immunoglobulin of Ochi with the gene therapy methods of Salser with a reasonable expectation of success of achieving the subject matter of challenged claims 1–4, 9, 11, 12, 15–20, and 33.

b. Claim 14

Petitioner specifically addresses the additional limitations of claim 14, asserting that Ochi teaches an antibody producing hybridoma. Petitioner contends that the ordinary artisan would have combined Salser and Ochi for the reasons discussed with respect to claims 1–4, 9, 11, 12, 15–20, and 33. Thus, for the reasons discussed above, we determine that Petitioner has not sufficiently demonstrated that the ordinary artisan would have had a reason

---

[6] In this regard, we agree with Patent Owner (Prelim. Resp. 57–58) that Salser teaches less than Bujard over which we instituted *inter partes* review in IPR2015-01624. IPR2015-01624, Paper 15. The Petitioner in the instant proceeding, Genzyme, filed a second petition challenging the ’315 patent, IPR2016-00460, that proffered the same challenges as were instituted in IPR2015-01624. IPR2016-00460 has been instituted and joined with IPR2015-01624. IPR2016-00460, Paper 12.

to combine the immunoglobulin of Ochi with the gene therapy methods of Salser with a reasonable expectation of success of achieving the subject matter of challenged claim 14.

iii. Conclusion

For the reasons set forth above, we determine that Petitioner has not established a reasonable likelihood that claims 1–4, 9, 11, 12, 14–20, and 33 are rendered obvious by the combination of Salser and Ochi.

E. Obviousness over Salser (Ex. 1002) and Southern (Ex. 1004)

Petitioner contends that claims 2, 18, and 20 are rendered obvious by the combination of the Salser and Southern. Pet. 51–54. Patent Owner disagrees. Prelim. Resp. 58–60.

i. Overview of Southern (Ex. 1004)

Southern teaches that there are two principal ways in which exogenous DNA may be introduced into mammalian cells. Ex. 1004, 327. The first is the use of Simian Virus 40 (SV40) as a transducing vector, and the second is direct introduction through the use of calcium phosphate precipitation, DEAE-dextran, or microinjection. *Id.*

Southern inserted a bacterial gene (neo) that confers resistance to neomycin-kanamycin antibiotics into SV40 hybrid plasma vectors, which allows for selection of transformed cells. *Id.*, Abstract, 328. The vectors "provide a way to cotransduce other genes whose presence and/or expression can not be selected." *Id.* at 338.

Specifically, Southern teaches that "[o]ne objective in seeking vectors with dominant selectable markers is to facilitate the introduction and maintenance of genes that do not confer a selection." *Id.* at 336. Thus, Southern transfected cells with DNAs that contained the neo and xanthine-

guanine phosphoribosyl transferase (gpt), and cells were selected for expression of either or both genes. *Id.* Cells were transformed with gpt and neo linked in a double marker plasmid (pSV2-neo-SVgpt), and with a mixture of pSC2-neo and pSV2-gpt plasmid DNAs. *Id.* Southern discloses that since the "schemes used to select for the expression of gpt and neo are complementary . . . experiments that exploit the possibilities of a double and dominant selection are now in progress. *Id.* at 339.

ii. Analysis

Petitioner contends to the extent that Salser fails to teach co-transformation of a single host cell with two vectors, Southern remedies that deficiency. Pet. 51. Petitioner argues that the ordinary artisan

> would have had a number of reasons to combine (1) Salser's disclosure of a mammalian host cell transformed with two genes—which as discussed above include the species of the heavy and light chain immunoglobulin genes—in a single vector with (2) the two-vector teaching in Southern . . . of the co-transformation of a mammalian host cell two genes of interest.

Id. at 51–52 (citing Ex. 1058 ¶ 86).

According to Petitioner, the ordinary artisan would have had a reasonable expectation of success given the teaching of the Salser patent "that heavy and light chain genes can be successfully co-expressed when they are present in a single transformed mammalian host cell, whether or not they are contained on the same vector or on separate DNA chains." *Id.* at 53 (citing Ex. 1058 ¶ 87).

Patent Owner responds that Petitioner only relies on Southern for its disclosure of two vectors. Prelim. Resp. 58. Patent Owner argues that Petitioner relies on its arguments made in its anticipation challenge that Salser discloses all of the elements of the challenged claims, including the

expression of immunoglobulins, and thus, this challenge fails for the same reasons as the anticipation challenge. *Id.*

We agree with Patent Owner that Southern does not remedy the deficiencies of Salser discussed above with respect to the anticipation rejection. We determine, therefore, that Petitioner has not sufficiently demonstrated that claims 2, 18, and 20 are rendered obvious by the combination of Salser and Southern.

iii. Conclusion

For the reasons set forth above, we determine that Petitioner has not established a reasonable likelihood that claims 2, 18, and 20 are rendered obvious by the combination of Salser and Southern.

F. Boss Patent[7] and Ochi 1983[8] Support a Finding of Obviousness

According to Petitioner, "[w]hen the alleged invention claimed by a patentee is also 'independently made' by another, 'near[ly] simultaneous' with the patentee's work, that is 'strong evidence of what constitutes the level of ordinary skill in the art' and is 'persuasive evidence that the [patent invention] 'was the product only of ordinary skill.'" Pet. 54 (alterations in original) (quoting *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l, LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010)).

Petitioner contends that both the Boss Patent and Ochi 1983 demonstrated co-expression of immunoglobulin heavy and light chains. *Id.*

---

[7] Boss et al., US Pat. No. 4,816,397, issued Mar. 28, 1989 (Ex. 1007) ("Boss Patent").

[8] Ochi et al., *Functional Immunoglobulin M Production After Transfection of Cloned Immunoglobulin Heavy and Light Chain Genes into Lymphoid Cells*, 80 PROC. NATL. ACAD. SCI. 6351–55 (1983) (Ex. 1035) ("Ochi 1983").

at 55–56. According to Petitioner, those references demonstrate that there was no prevailing mindset that only one polypeptide could be expressed per host cell, and also supports the conclusion that the "purported invention of the '415 patent was merely the product of ordinary skill." *Id.* at 56.

As noted by the Federal Circuit in *Geo. M. Martin Co.*, simultaneous invention is not determinative of statutory obviousness. *Geo. M. Martin Co.*, 618 F.3d at 1306. In the instant proceeding, as discussed above, Petitioner has not established a reasonable likelihood that the challenged claims are rendered obvious over the cited prior art. That deficiency is not rectified with Petitioner's contention that the invention of the challenged claims was made nearly simultaneously and independently by two other groups, represented by the Boss Patent and Ochi 1983.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in any of its challenges of claims 1–4, 9, 11, 12, 14–20, and 33.

IV. ORDER

In consideration of the foregoing, it is hereby ordered that the Petition is *denied*.

PETITIONER:

Richard McCormick
Brian Nolan
MAYER BROWN LLP
rmccormick@mayerbrown.com
BNolan@mayerbrown.com

PATENT OWNER:

David L. Cavanaugh
Heather M. Petruzzi
WILMER CUTLER PICKERING HALE AND DORR LLP
David.Cavanaugh@wilmerhale.com
Heather.Petruzzi@wilmerhale.com

Jeffrey P. Kushan
iprnotices@sidley.com

Adam R. Brausa
abrausa@durietangri.com